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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/808,678	03/25/2004	Jeremy Green	VPI/02-137 US	6199

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VERTEX PHARMACEUTICALS INC.
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EXAMINER	
CHANDRAKUMAR, NIZAL S	
ART UNIT	**PAPER NUMBER**
1625	

MAIL DATE	DELIVERY MODE
07/18/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/808,678	GREEN ET AL.	
	Examiner	Art Unit	
	Nizal S. Chandrakumar	1625	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 2 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 May 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *47,49,50,52,53,59-68 and 71-101* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *47, 49, 50, 52, 53, 59, 60-68, and 71-101* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This application filed 03/25/2004 claims benefit of 60/460,042 04/03/2003.

Claims 47, 49-54, 56 and 59-10 were pending.

Applicant's response filed 05/18/2007 to office action filed 02/22/2007 is acknowledged.

Applicants amend claims 47, 49, 50, 53, 59, 60, 62, 64 and 68 are amended; cancelled claims 51, 54, 56 and 69-70.

Claims 47, 49, 50, 52, 53, 59, 60-68, and 71-101 are pending.

The indicated allowability of claims 65-99 is withdrawn for the following reasons.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 47, 49, 50, 52, 53, 59-68, 71-101 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The instant specification does not adequately describe the nexus between the activity of the protein kinase receptor activity and a useful treatment of a disease/condition. It is not seen where the instant specification adequately describes the nexus between the inhibition of the protein kinase receptor and a useful treatment of a single disease or condition.

Claims 47, 49, 50, 52, 53, 59-68, 71-101 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described

in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue". These factors include 1) the breadth of the claims, 2) the nature of the invention, 3) the state of the prior art, 4) the level of one of ordinary skill, 5) the level of predictability in the art, 6) the amount of direction provided by the inventor, 7) the existence of working examples, and 8) the quantity of experimentation needed to make or use the invention based on the content of the disclosure. In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

1) The breadth of the claims,
2) The nature of the invention,
3) The state of the prior art,
4) The level of one of ordinary skill,
5) The level of predictability in the art,
6) The amount of direction provided by the inventor,
7) The existence of working examples,
8) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

The nature of the invention: The inventions are drawn to compositions containing chromene-oxime derivatives and their use in diagnosis and treatment of various disease states wherein protein kinases are implicated.

The state of the prior art: The state of the prior art is that it involves screening in vitro and in vivo to determine which compounds exhibit the desired pharmacological activities (i.e. what compounds can treat which specific disease). There is no absolute predictability even in view of the seemingly high level of skill in the art. The existence of these obstacles establishes that the contemporary knowledge in the art would prevent one of ordinary skill in the art from accepting any therapeutic regimen on its face.

The predictability in the art: It is noted that the pharmaceutical art is unpredictable, requiring each embodiment to be individually assessed for physiological activity. In re Fisher, 427 F. 2d 833, 166 USPQ 18 (CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. In the instant case, the instantly claimed invention is highly unpredictable since one skilled in the art would recognize that in regards to the therapeutic effects of all

diseases, whether or not the inhibition of protein kinase receptors would make a difference in the disease. Hence, in the absence of a showing of a nexus between any and all known diseases and the inhibition of protein kinase receptors, one of ordinary skill in the art is unable to fully predict possible results from the administration of the compound of claim 1 due to the unpredictability of the role of inhibition of protein kinase receptors. Those of skill in the art recognize that in vitro assays and or cell-cultured based assays are generally useful to observe basic physiological and cellular phenomenon such as screening the effects of potential drugs. However, clinical correlations are generally lacking. The greatly increased complexity of the in vivo environment as compared to the very narrowly defined and controlled conditions of an in- vitro assay does not permit a single extrapolation of in vitro assays to human diagnostic efficacy with any reasonable degree of predictability. In vitro assays cannot easily assess cell-cell interactions that may be important in a particular pathological state. Furthermore it is well known in the art that cultured cells, over a period time, lose phenotypic characteristics associated with their normal counterpart cell type. Freshney (Culture of Animal Cells, A Manual of Basic Technique, Alan R. Liss, Inc., 1983, New York, p4) teach that it is recognized in the art that there are many differences between cultured cells and their counterparts *in vivo*. These differences stem from the dissociation of cells from a three-dimensional geometry and their propagation on a two-dimensional substrate. Specific cell interactions characteristic of histology of the tissue are lost. The culture environment lacks the input of the nervous and endocrine systems involved in homeostatic regulation *in vivo*. Without this control, cellular metabolism may be more constant *in vitro* but may not be truly representative of the tissue from which the cells were derived. This has often led to tissue culture being regarded in a rather skeptical light (p. 4, see Major Differences *In Vitro*). Further, although drawn specifically to cancer cells, Dermer (Bio/Technology, 1994, 12:320) teaches that, "petri dish cancer" is a poor representation of malignancy, with characteristics profoundly different from the human disease Further, Dermer teaches that when a normal or malignant body cell adapts to immortal life in culture, it takes an evolutionary type step that enables the new line to thrive in its artificial environment. This step transforms a cell from one that is stable and differentiated to one that is not. Yet normal or malignant cells *in vivo* are not like that. The reference states that evidence of the contradictions between life on the bottom of a lab dish and in the body has been in the scientific literature

for more than 30 years. Clearly it is well known in the art that cells in culture exhibit characteristics different from those *in vivo* and cannot duplicate the complex conditions of the *in vivo* environment involved in host-tumor and cell-cell interactions.

The presence or absence of working examples: The specification provides working examples of enzyme inhibition assays for the ability (Ki values) of the test compounds to inhibit several protein kinases *in vitro*.

The amount of direction or guidance present: The working examples (page 69-77 of the specification) indicate that 'certain compounds of the invention have Ki values < 1μM). The guidance present in the specification is that of the compounds that are tested, some work, some don't work, and some work to a weak extent at the in vitro level. Very similar compounds have been shown to possess widely different activities (less than one micro rmolar includes pico molar and thus the range is in orders of magnitude). In addition, it is not seen where the specification provides information regarding toxicity and or PK/PD profile of these compounds that would be necessary for the intended use of these compounds. Page one of the specification states that protein kinase is thought to play an important role in a variety of diseases. The specification does not seem to enable a correlation between the inhibition of protein kinase receptors with compounds of the formula I and the treatment of any and all diseases with compounds of the formula I.

The breadth of the claims: The claims are drawn to the treatment of any and all diseases mediated by the protein kinase receptor with the compounds of formula I.

The quantity of experimentation needed: The quantity of experimentation needed is undue. One skilled in the art would need to determine what diseases out of all known diseases would be benefited by the inhibition of protein kinase receptors and then would further need to determine which of the claimed compounds would provide treatment of the disease.

One skilled in the art would need to determine what diseases out of all known diseases would be benefited by the mediation of inhibition of protein kinases and then would further need to determine which of the claimed compounds would provide treatment of the disease. The instant compounds (some of them) exhibit inhibition of kinase receptors at Ki < 1μM. As discussed above, it is well known in the art

that in vitro activity is not necessarily a predictor of in vivo efficacy. There is no teaching in the specification or working examples to show how the instant compounds with such an in vitro profile have utility in treating diseases in which inhibition of the protein kinases is implicated. Therefore, in the absence of information relating to efficacy (such as EC50 or ED50), toxicity (such as LD50) and PK/PD for the compounds of the formula I (or in combination with other active pharmaceutical ingredients) it would be difficult to predict what compounds within the broad genus of formula I with wide possibilities for substituents would possess the desired activity, thus creating an extraordinary amount of trial and error experimentation to identify the compound of formula I with desirable biological property.

The level of the skill in the art: The level of skill in the art is high. However, due to the unpredictability in the pharmaceutical art, it is noted that each embodiment of the invention is required to be individually assessed for physiological activity by in vitro and in vivo screening to determine which compounds exhibit the desired pharmacological activity and which diseases would benefit from this activity.

Thus, the specification fails to provide sufficient support of the broad use of the compounds of formula I for the treatment of any disease. As a result necessitating one of ordinary skill to perform an exhaustive search for which diseases can be treated by which compound of claim 1 in order to practice the claimed invention.

Genentech Inc. v. Novo Nordisk A/S (CA FC) 42 USPQ2d 1001, states that "a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion" and "[p]atent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable".

Therefore, in view of the Wands factors and In re Fisher (CCPA 1970) discussed above, to practice the claimed invention herein, one of ordinary skill in the art would have to engage in undue experimentation to test which diseases can be treated by the compounds of the instant claims, with no assurance of success.

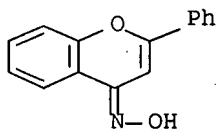
Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim 47 and dependent claims are rejected under 35 U.S.C. 102(b) as being anticipated by Gulati et al. (Current Science (1936, 5, 75).

Gulati et al. teach



corresponding to compound of formula I wherein

R1 = (L)mAr1 wherein m=0, Ar1 is 6-membered optionally substituted monocyclic ring (also Ar1 is substituted with Z-Rx wherein Z is a bond, Rx is R' wherein R' is hydrogen),

R2 = hydrogen,

T = CH, R3 being hydrogen,

A1 = A2 = A3 = CH, R4 being (L)mR wherein m=0 and R=H.

Also see compare structures I-7 and I-15, page 20 of specification.

Examiners response to Applicant's Remarks

Rejections under Claim Rejections - 35 USC § 112: The applicant traverses the rejection of claims 52-54 and 56 for lacking enablement. The applicant points out that the protein fragment HGF has shown inhibitory effect in a growth of human tumor cell lines in a mouse model. In addition, the applicant points out the effects of a small molecule inhibitor (PHA-665752) of C-Met in a mouse model in a particular cell line. Taken together, the applicant assert, these date show that an inhibitor of c-Met would inhibit cancer cell growth. This argument is not persuasive because the pharmaceutical art is

unpredictable, requiring each embodiment to be individually assessed for physiological activity. This individual assessment is necessary because of the therapeutically useful vivo activity any compound depends to a great extent on the PK/PD parameters as well as therapeutic index of that particular compound.

Applicants state that a skilled artisan would be able to discern an appropriate dosage and method of use based upon the information provided in the specification pages 49-50. What are presented in page 49-50 are potential methods of formulations. Given only the Ki values for inhibition, with the absence of parameters such as the afore-mentioned therapeutic index etc., one skilled in the art would be unable to formulate a composition containing a compound of the formula I which would have the desirable biological activity.

The applicant has deleted the terms ('...agents") that were at issue from claims 49 and 53. Therefore the rejections with regards to the terms 'chemotherapeutic or anti-proliferative agent' are withdrawn.

The inclusion of specific approved drugs useful in a potential combination therapy in the claims 49 and 53 does not negate the rejections set forth in this office rejection (see above).

Previously presented Rejections:

Claim Rejections - 35 USC § 112

The claim rejections under 35 USC § 112, first paragraph are maintained except rejections with regards to the above-mentioned 'agents'.

Applicant's amendments overcome the claim rejection under 35 USC § 112, second paragraph.

Claim Rejections - 35 USC § 102

Applicant's amendments overcome the claim rejection under 35 USC § 102.

Conclusion

Applicant's amendments overcome part of the rejections set forth in the office action filed 02/22/2007. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is

reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nizal S. Chandrakumar whose telephone number is 571-272-6202. The examiner can normally be reached on 8.30 am – 5 pm Monday- Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet Andres can be reached at 571-272-0867 or Primary Examiner D. Margaret Seaman can be reached at 571-272-0694. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Nizal S. Chandrakumar

D. MARGARET SEAMAN
PRIMARY EXAMINER